Non-self-sufficiency as a primary outcome measure in ALS trials

Non Self-sufficiency as a primary outcome measure in ALS trials

Running title: Non Self-sufficiency as an outcome measure in ALS trials

Benoît Marin[1,2,3,4], Elisa Bianchi[4], Elisabetta Pupillo[4], Giancarlo Logroscino[5], Adriano Chiò[6], Pierre Marie Preux[1,2,3], and Ettore Beghi[4]

1. INSERM UMR1094, Tropical Neuroepidemiology, Limoges, France ;
2. University of Limoges, School of Medicine, Institute of Neuroepidemiology and Tropical Neurology, CNRS FR 3503 GEIST, Limoges, France;
3. CHU Limoges, Centre d'Epidémiologie de Biostatistique et de Méthodologie de la Recherche, France;
4. Laboratory of Neurological Disorders, Department of Neuroscience, IRCCS Institute for Pharmacological Research Mario Negri, Milano, Italy;
5. Department of Neuroscience, University of Bari, Italy;
6. ALS Centre, 'Rita Levi Montalcini' Department of Neuroscience, University of Torino, AOU ~~San Giovanni Battista~~Città della Salute e della Scienza, Torino, Italy.

Corresponding author: Dr Ettore Beghi

IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"

Via G. La Masa, 19 Milano, ITALY

phone: 02/39014542; fax: 02/39001916

e-mail: ettore.beghi@marionegri.it

Word count : 2431

Abstract

Objective: To assess non-self-sufficiency (NSS) in ALS as an outcome measure in therapeutic trials. Methods: Using data from the control arm of two randomized trials and an observational study, NSS (score 2 or less in the ALS-FRS-R items for swallowing, cutting food and handling utensils, or walking) was compared to the total ALS-FRS-R score, forced vital capacity (FVC), and survival at selected time points until death or 48 weeks. Results: Of 82 self-sufficient (SS) patients at baseline, 32 (39.0%) became NSS at 4 weeks and 72 (87.8%) at the end of follow-up. A significant association was found between NSS, ALSFRS-R score and FVC at 24, 36, 48 weeks. 34 subjects died (41.5%). As compared to SS patients (median survival, 27.9 months), individuals becoming NSS at 4 weeks were at increased risk to die during follow-up (median survival, 23.6 months, p=0.02). NSS status at 4 weeks predicted survival even after adjustment for ALS-FRS-R total score, age, sex, site of onset, BMI, and FVC.“Walking” was the only predictor of survival when adjusting for all covariates. Conclusions: NSS status is a possible outcome measure in ALS to investigate short-term efficacy of treatments of ALS.

Keywords

Amyotrophic lateral sclerosis, non self-sufficiency, outcome measures, clinical trials.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease ending in death or severe disability in 3-5 years from symptom onset (1). Time to death and functional decline are the preferred measures to assess the prognosis of the disease and the effects of treatments. The guideline issued by the European Medicines Agency (EMA) on the clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (2) requires either survival time or ALS Functional Rating Scale in its original (ALS-FRS) (3) or revised version (ALS-FRS-R) [4] to be used as primary outcome measure. Secondary measures include the assessment of functional ability, muscle strength, respiratory function and quality of life.

The ALS-FRS-R (3) is the most widely used instrument to measure the progression of the disease and the degree of functional impairment in ALS. The ALS-FRS-R has been confirmed highly reliable (5, 6) and is accepted as a valuable outcome measure in clinical trials (7). However, the decline measured by the ALS-FRS-R has been found non-linear in a substantial number of patients (8). Furthermore, the scale is insensitive to change (9) particularly in patients with advanced disease (10). This limitation led investigators to suggest collapsing the five level ratings into three levels (11) or to add new items to measure abilities in patients with advanced disease (12). Then, in spite of a consensus among clinicians that a change of 20% or greater in the slope is a surrogate of a clinically significant functional deterioration (13), the total score of the scale (the measure used in clinical trials as a marker of functional impairment) does not indicate which functions are lost and, most importantly, if the patient lost his/her self-sufficiency.

Markers of self-sufficiency (swallowing, cutting food and handling utensils, or walking), as measured by the ALS-FRS-R scale, were recently used as primary outcomes in two randomized trials assessing the efficacy of Acetyl-L-carnitine and Lithium in ALS (14, 15). Non self-sufficiency (NSS) was defined as a score of 2 or lower on at least one of the three ALSFRS-R items over 12 months. However, this measure requires validation. On this background, the main aim of the present study was to assess the sensitivity to change of NSS status and of each of its three items separately.

More specifically, we decided to (i) describe the risk of a patient with ALS to become non self-sufficient (NSS) during follow-up, (ii) verify whether NSS status was associated with the total ALS-FRS-R score and to other measures of functional disability, (iii) identify if the ALS-FRS-R items indicating self-sufficiency are prognostic factors for survival of ALS patients, and (iv) among items of ALS-FRS-R, which items are prognostic indicators.

Material and Methods

Patients

Included were patients enrolled in the placebo arm of the randomized trial on Acetyl-L-carnitine (14), in the subtherapeutic arm (pseudo placebo) of the randomized trial on Lithium (15), and in the context of an observational study of the outcome of ALS in a tertiary center. Patients were accepted for the analysis only if self-sufficient at baseline (time of inclusion) in the study.

Follow-up

Patients were followed for 48 weeks or until death, whichever came first. If possible, vital status was investigated for up to 68 months in patients who were still alive at the end of the trial.

Data collection

The following data were recorded from the trial files: Age, sex, site of onset (spinal vs. bulbar), body mass index (BMI) at baseline, forced vital capacity (FVC) at baseline, 24, 36 and 48 weeks, and ALS-FRS-R scale at baseline and at 4, 12, 24, 36 and 48 weeks, and NSS status (ie, a score of 2 or lower on at least one of the ALS-FRS-R items for swallowing, cutting food and handling utensils, or walking) at baseline, and at 4, 12, 24, 36, and 48 weeks.

Ethics

The ethics committees of the participating centres approved both trials. As anonymized data were obtained from the trial databases, no additional ethical approval was required.

Statistical analysis

Descriptive statistics are given for all the baseline variables, with frequency, percentages, medians and interquartile range(IQR) as appropriate. The NSS status and the ALS-FRS-R score are presented at baseline and at each time point during follow-up. NSS and demographic and main clinical variables were correlated using the Mann-Whitney, Chi-square or Fisher exact test where appropriate. The change of NSS status over time has been assessed using actuarial methods. The association between each variable at baseline and NSS status during follow-up was tested with Cox's proportional hazards function models. Survival was assessed using Kaplan-Meier curves. The association between NSS status at 4 weeks and survival was evaluated using the Log-rank test. The prediction of survival based on NSS status at 4 weeks was tested using univariate and multivariate models, the latter including age at inclusion, sex, site of onset, BMI, FVC and ALSFRS-R at baseline as covariates. Each item of the ALS-FRS-R scale was assessed separately in univariate and multivariate Cox models. Abnormal values scored 2 or less for each item, except for item 12 (respiratory insufficiency) for which abnormal values were any score lower than 4. Statistical significance was set at the 5% level ($p<0.05$). Statistical analyses were performed using the SAS statistical package (version 9.2; SAS Institute, Cary, NC).

Results

The sample included 82 patients (53 men and 29 women) aged 33 to 76 years (median 61.5 years, IQR 54.7-68.0) (Table 1). Patients with bulbar-onset ALS were 30.5%. At study entry, disability was modest and nutritional status was excellent in most cases.

Loss of self-sufficiency during follow-up

Twenty-two patients (39.0%) became NSS at 4 weeks and 72 (87.8%) at the end of follow-up. There was no difference between SS and NSS patients as regards age ($p=0.27$), sex ($p=0.88$) and site of onset ($p=0.71$). The cumulative time-dependent probability of remaining SS decreased with

time and was 19.9% at 24 weeks and 7.8% at 48 weeks (Figure 1). None of the baseline variables was associated with NSS status during follow-up (Table 2).

Association between NSS status and other measures of functional disability

As indicated in Table 3, when comparing at each time point functional status of NSS and SS patients, the ALS-FRS-R total score was consistently lower in NSS than in SS subjects. In contrast, there was no association between NSS status and FVC at 24 and 36 weeks. When comparing at each time the clinical status of SS patients to that of subjects who became NSS at 4 weeks, similar results were obtained for ALS-FRS-R total score. In this subpopulation, an association was found between NSS and FVC at 24, 36 and 48 weeks.

Loss of self-sufficiency and survival

During follow-up, 34 subjects died (41.5%), 11 within the first 48 weeks. As compared to SS patients, individuals becoming NSS at 4 weeks had a 2.28 increased risk to die during follow-up (95% confidence interval, CI 1.15-4.59). The median survival time in NSS patients was 23.6 months (95% CI 8.2-40.7) for NSS and 27.9 months (95% CI 21.8-54.4) in SS individuals (p=0.02, Figure 2). NSS status at 4 weeks predicted survival (HR 2.77, 95% CI 1.26-6.15), even after adjustment for ALS-FRS-R total score, age, sex, site of onset, BMI, and FVC (Table 5).

NSS status during the entire follow-up (time varying covariate) was also assessed as an explanatory variable for survival. The association was not statistically significant both in univariate and in multivariate analysis (HR 2.7 95% CI 0.60-12.34, p=0.20) after adjusting for the same covariates (Table 5).

Association between survival and each ALS-FRS-R item

On univariate analysis, none of the 12 items of the ALS-FRS-R scale, if found abnormal, was associated with death (Table 6). When adjusting for all ALS-FRS-R items (multivariate model 1), “walking” was the only item predicting survival. Another item (“cutting food and handling utensils”) was of borderline significance (p=0.08).

Discussion

In this study, NSS status was found to be sensitive to the change of the clinical state of ALS patients as being associated with the entire ALS-FRS-R score and to other measures of functional disability. NSS at 4 weeks also predicted survival with a significant difference in the median survival time between SS and NSS patients, which was confirmed after adjustment on confounding factors. One of its components (ie, walking) was the only independent prognostic predictor for survival. Another component (cutting food/handling utensils) resulted of borderline significance. We can hypothesize that a modification in the occurrence of NSS (mostly represented by lack of ambulation) could result in a modification in the survival of ALS patients. Hence, NSS status can be proposed as a surrogate endpoint in ALS phase II and III trials. It has the advantage of being by itself clinically relevant, an excellent quality for a surrogate marker. Then, its interpretation is easy in contrast with other score-based outcomes.

As indicated in this study, the outcome of ALS measured by loss of self-sufficiency is rapid (subjects remaining SS during time being 61.0% at 4 weeks and 19.9% at 24 weeks). Thus, NSS status can be used as a variable with high probability of occurrence within the time limits of a clinical trial.

The association between NSS and the total ALS-R score and, to some extent the FVC score, further confirms the role of self-sufficiency as a marker of disease progression. When we compared NSS status to a subscore of the ALS-FRS-R scale (calculated excluding the three measures of self-sufficiency), the association remained unchanged (data not shown).

Interestingly, except for walking and, to some extent, cutting food/handling utensils, none of the other scale items were associated with survival. This reinforces the clinical relevance of the NSS status as a prognostic predictor and seems to explain that the prognostic significance of the ALS-FRS-R scale is mostly driven by these two subscales.

Among the three markers of self-sufficiency, swallowing was not found to predict survival. This can be explained by the small number of cases with dysphagia at 4 weeks (n=6). The same holds

true for other bulbar signs (except for speech), and signs of respiratory insufficiency. Most patients included in this study had modest disability and excellent nutritional status at 4 weeks. Thus, the prognostic role of dysphagia cannot be entirely excluded here because of the small sample size. The lack of association between loss of self-sufficiency and relevant demographic and clinical variables (except for age) seems to support the robustness of this outcome measure, which is independent from the main prognostic predictors. Then, the detection of NSS as an early (4-week) predictor of mortality supports the role of self-sufficiency as a valuable end-point when testing the early effects of an investigational treatment.

Alternative measures of disease progression have been recently developed (16, 17). However, compared to these markers, loss of self-sufficiency is a simple measure based on the assessment of selected functions having strong impact on fine and gross motor activities and on nutritional state. Compared to the entire ALS-FRS-R scale, this marker of disease progression can be used on an individual basis to identify potential responders to experimental treatments.

The study has limitations that must be highlighted. First of all, only one of the three items seems an independent predictor of disease progression and survival. The third component (swallowing) may deserve further investigation by examining patients in late stages of the disease. Second, we tested NSS status (the sum of three subscores of the ALS-FRS-R scale) against the total ALS-FRS-R score. An association may be thus expected as the two scores are not totally independent. However, other independent measures of disease severity, like FVC and death, have been found to be significantly associated with loss of self-sufficiency. Third, the sample size is small and may prevent the detection of otherwise significant associations. A larger, more representative and independent ALS population should be evaluated to confirm the validity of NSS status as a prognostic marker. Fourth, survival of patients after the end of the trials was tentatively monitored, but was not possible for all patients. Firth, NSS status was found to predict survival at 4 weeks but not when considered along the entire follow-up. As the adjusted hazards ratio was 2.77 at 4 weeks and 2.70 for NSS as time varying covariate, the non-significant risk might be explained by a lack of

power of this analysis. A study in a larger sample is again needed to confirm or disprove the present findings.

Conclusions

NSS status is a promising outcome measure in randomized trials in ALS patients, which could be used as a primary end-point to investigate short-term efficacy of investigational drugs and other treatments. ALS-FRS-R scale is still a recommended instrument to monitor disease progression and, as such, it cannot be at present replaced. However, further studies are needed in large and representative ALS populations to verify whether some subscales or individual items should be removed from the scale as being non-influential in marking the outcome of ALS.

Acknowledgements

The study could be performed thanks to the access to the data of two published trials. The authors and collaborators of these studies are to be acknowledged:

Lithium trial (Neurology 2010;75:619-25)

Authors: Chiò A, Borghero G, Calvo A, Capasso M, Caponnetto C, Corbo M, Giannini F, Logroscino G, Mandrioli J, Marcello N, Mazzini L, Moglia C, Monsurrò MR, Mora G, Patti F, Perini M, Pietrini V, Pisano F, Pupillo E, Sabatelli M, Salvi F, Silani V, Simone IL, Sorarù G, Tola MR, Volanti P, Beghi E; LITALS Study Group.

LITALS Study Group: Tortelli R, D'Errico E, Bartolomei I, Barbarossa E, Depau B, Costantino E, D'Amico E, Uncini A, Manzoli C, Quatrale R, Sette E, Montanari E, Merello M, Zarcone D, Mascolo M, Vignolo M, Messina S, Morelli C, Marinou K, Papetti L, Lunetta C, Gorni K, De Cicco D, Pipia C, Sola P, Georgoulopoulou E, Sagnelli A, Tedeschi G, Oggioni G, Nasuelli N, D'Ascenzo C, Cima V, Aiello M, Rizzi R, Rinaldi E, Luigetti M, Conte A, Torzini A, Greco G, Mutani R, Fuda G, Tommasi MA.

Acetyl-L-carnitine trial (Amyotroph Lateral Scler Frontotemporal Degener.2013;14:397-405).

Authors: Beghi E, Pupillo E, Bonito V, Buzzi P, Caponnetto C, Chiò A, Corbo M, Giannini F, Inghilleri M, Bella VL, Logroscino G, Lorusso L, Lunetta C, Mazzini L, Messina P, Mora G, Perini M, Quadrelli ML, Silani V, Simone IL, Tremolizzo L; Italian ALS Study Group.

Italian ALS Study Group: Samarelli V, Tortelli R, D'Errico E, Merello M, Tavernelli F, Mancardi GL, Mascolo M, Bendotti C, Buratti M, Floriani I, Giordano L, Giussani G, Maderna L, Maestri E, Marinou K, Mennini T, Messina S, Morelli C, Papetti L, Rizzo A, Ticozzi N, Verde F, Ferrarese C, Marzorati L, Testa L, Valentino F, Frasca V, Giacomelli E, Casali S, Malentacchi M, Calvo A, Cammarosano S, Moglia C, Cavallo E, Fuda G.

Disclosure of Interests

Drs Marin, Bianchi and Logroscino report no conflicts of interest.

Dr Pupillo has received funding from the American ALS Association and Italian Ministry of Health for data management and data monitoring of an observational study protocol. She receive funding from Italian Drug Agency (AIFA) for data monitoring and study management of randomized clinical trial. Dr Chiò reports grants from European Union, grants from Italian Ministry of Health, outside the submitted work; and has served on scientific advisory boards for Biogen Idec, and Cytokinetics, Inc, and Italfarmaco.

Dr Preux ….

Dr Beghi has received money for board membership by VIROPHARMA and EISAI; has received funding for travel and speaker honoraria from UCB-Pharma, GSK and has for educational presentations from GSK; has received grants for research activities from the Italian Drug Agency, Italian Ministry of Health, Sanofi-Aventis and the American ALS Association.

References

1. Beghi E, Chio A, Couratier P, Esteban J, Hardiman O, Logroscino G, et al. The epidemiology and treatment of ALS: focus on the heterogeneity of the disease and critical appraisal of therapeutic trials. Amyotroph Lateral Scler 2011;12:1-10.
2. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS). 2014 [cited 2014 July 17th]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147005.pdf.
3. ACTS Study Group. The Amyotrophic Lateral Sclerosis Functional Rating Scale. Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. The ALS CNTF treatment study (ACTS) phase I-II Study Group. Arch Neurol 1996;53:141-7.
4. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169:13-21.
5. Kaufmann P, Levy G, Montes J, Barsdorf AI, Battista V, Arbing R, et al. Excellent inter-rater, intra-rater, and telephone-administered reliability of the ALSFRS-R in a multicenter clinical trial. Amyotroph Lateral Scler 2007;8:42-6.
6. Maier A, Holm T, Wicks P, Steinfurth L, Linke P, Münch C, et al. Online assessment of ALS functional rating scale compares well to in-clinic evaluation: a prospective trial. Amyotroph Lateral Scler 2012;13:210-6.
7. Leigh PN, Swash M, Iwasaki Y, Ludolph A, Meininger V, Miller RG, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord 2004;5:84-98.
8. Gordon PH, Cheng B, Salachas F, Pradat PF, Bruneteau G, Corcia P, et al. Progression in ALS is not linear but is curvilinear. J Neurol 2010;257:1713-7.

9. Traynor BJ, Zhang H, Shefner JM, Schoenfeld D, Cudkowicz ME; NEALS Consortium. Functional outcome measures as clinical trial endpoints in ALS. Neurology 2004;63:1933-5.
10. Voustianiouk A, Seidel G, Panchal J, Sivak M, Czaplinski A, Yen A, et al. ALSFRS and appel ALS scores: discordance with disease progression. Muscle Nerve 2008;37:668-72.
11. Franchignoni F, Mora G, Giordano A, Volanti P, Chiò A. Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis. J Neurol Neurosurg Psychiatry 2013;84:1340-5.
12. Wicks P, Massagli MP, Wolf C, Heywood J. Measuring function in advanced ALS: validation of ALSFRS-EX extension items.Eur J Neurol 2009;16:353-9.
13. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, Cudkowicz ME. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler 2010;11:178-80.
14. Beghi E, Pupillo E, Bonito V, Buzzi P, Caponnetto C, Chiò A, et al. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS.Amyotroph Lateral Scler Frontotemporal Degener 2013;14:397-405.
15. Chio A, Borghero G, Calvo A, Capasso M, Caponnetto C, Corbo M, et al. Lithium carbonate in amyotrophic lateral sclerosis: lack of efficacy in a dose-finding trial. Neurology 2010;75:619-25.
16. Chio A, Hammond ER, Mora G, Bonito V, Filippini G. Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2013 Dec 13. doi: 10.1136/jnnp-2013-306589. [Epub ahead of print]
17. Roche JC, Rojas-Garcia R, Scott KM, Scotton W, Ellis CE, Burman R, et al. A proposed staging system for amyotrophic lateral sclerosis. Brain 2012;135:847-52.

Table 1. Demographical and clinical characteristics of the sample at baseline (n=82)

Variables		Median or frequency	Interquartile range or percentage
Quantitative			
Age		61.5	54.7-68.0
ALSFRS-R score		42.0	39.0-44.0
FVC score (% of predicted)		84.9	77.7-97.4
BMI		24.5	22.1-26.2
Qualitative			
Sex	Female	29	35.4
	Male	53	64.6
Site of onset	Bulbar	25	30.5
	Spinal	57	69.5

BMI: Body mass index; FVC: Forced vital capacity.

Table 2. NSS status during follow-up and baseline characteristics. Univariate Cox analysis

Variable		HR	95%CI	p-value
Sex	Male	1.00 (ref)		
	Female	1.26	0.78 - 2.05	0.34
Site of onset	Spinal	1.00 (ref)		
	Bulbar	1.10	0.67 - 1.82	0.70
Age	5 year increase	1.03	0.92 - 1.15	0.64
FVC (% of predicted)	10% increase	0.97	0.81 - 1.16	0.71
BMI Class	Malnutrition	1.10	0.15 - 8.04	0.64
	Normal	1.00 (ref)		
	Overweight	1.35	0.81 - 2.25	
	Obese	1.48	0.58 - 3.74	

NSS: Non self-sufficient; HR: Hazards ratio; 95% CI: 95% Confidence interval;
BMI: Body mass index: (i) Malnutrition: BMI <18.5 if age <70 years orBMI<21 if age≥70 years; (ii) Normal: 18.5≤BMI<25 if age <70 years or 21≤BMI<27 if age ≥70 years; (iii) Overweight: 25≤BMI<30if age <70 years or 27≤BMI<30 if age ≥70 years; (iv) Obesity:BMI≥30, FVC: Forced vital capacity.

Table 3. ALS-FRS-R and FVC scores in SS and NSS patients at various time points during follow-up

Timepoint	Scale/Measure of disease progression	Self-sufficiency	N	Median	IQR	p-value
4 weeks	ALS-FRS-R (total)	SS	50	42.0	40.0 - 44.0	<0.0001
		NSS	32	36.5	33.0 - 39.5	
12 weeks	ALS-FRS-R (total)	SS	30	42.0	40.0 - 44.0	<0.0001
		NSS	50	35.5	29.0 - 39.0	
24 weeks	ALS-FRS-R (total)	SS	15	41.0	39.0 - 44.0	<0.0001
		NSS	53	34.0	28.0 - 37.0	
	FVC (% predicted)	SS	9	78.0	73.6 - 82.0	0.1316
		NSS	34	68.7	58.8 - 80.9	
36 weeks	ALS-FRS-R (total)	SS	10	40.0	39.0 - 44.0	0.0002
		NSS	45	32.0	25.0 - 36.0	
	FVC (% predicted)	SS	8	77.5	68.8 86.5	0.0574
		NSS	26	63.2	48.6 - 73.0	
48 weeks	ALS-FRS-R (total)	SS	4	41.0	38.0 - 43.5	0.0040
		NSS	40	27.5	21.0 - 32.5	
	FVC (% predicted)	SS	3	78.0	78.0 - 92.0	0.0435
		NSS	24	48.5	40.5 - 71.0	

SS: Self-sufficient; NSS: Non self-sufficient; FVC: Forced vital capacity; IQR: interquartile range.

Table 4. ALS-FRS-R and FVC scores at various time points for SS patients and patients who became NSS at 4 weeks

Time point	Scale/Measure of disease progression	Self-sufficiency	N	Median	IQR	p-value
4 weeks	ALS-FRS-R (total)	SS	50	42.0	40.0 - 44.0	<0.0001
		NSS	32	36.5	33.0 - 39.5	
12 weeks	ALS-FRS-R (total)	SS	30	42.0	40.0 - 44.0	<0.0001
		NSS	29	31.0	26.0 - 37.0	
24 weeks	ALS-FRS-R (total)	SS	15	41.0	39.0 - 44.0	<0.0001
		NSS	23	28.0	19.0 - 36.0	
	FVC (% predicted)	SS	9	78.0	73.6 - 82.0	0.0182
		NSS	14	63.3	45.5 - 71.0	
36 weeks	ALS-FRS-R (total)	SS	10	40.0	39.0 - 44.0	0.0011
		NSS	17	27.0	23.0 - 33.0	
	FVC (% predicted)	SS	8	77.5	68.8 - 86.5	0.0123
		NSS	10	55.8	36.2 - 66.0	
48 weeks	ALS-FRS-R (total)	SS	4	41.0	38.0 - 43.5	0.0189
		NSS	13	26.0	21.0 - 31.0	
	FVC (% predicted)	SS	3	78.0	78.0 - 92.0	0.0347
		NSS	9	46.0	42.4 - 49.0	

SS: Self-sufficient; NSS: Non self-sufficient; FVC: Forced vital capacity; IQR: interquartile range.

Table 5. Association between NSS status and survival in univariate and multivariate analysis

Variable		HR	95%CI	p-value
NSS at 4 weeks	Univariate	2.28	1.13 - 4.59	0.021
	Multivariate (after adjustment on age, gender, bulbar form, BMI, FVC, ALSFRS-R)	2.77	1.26 - 6.15	0.013
NSS during the entire follow-up	Univariate	2.81	0.64 - 12.42	0.173
	Multivariate (after adjustment on age, gender, BMI, FVC, ALSFRS-R)	2.70	0.60 - 12.34	0.202

NSS: Non self-sufficient; BMI: Body mass index; FVC: Forced vital capacity; HR: Hazards ratio; 95% CI: 95% Confidence interval.

Table 6. Association between abnormal ALS-FRS-R items and survival

Variables		Univariate analysis			Multivariate analysis model 1			Multivariate analysis model 2		
		Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value	Hazard Ratio	95%CI	p-value
ALS-FRS-R item	Abnormal value (%)*									
1. Speech	16 (19.5)	0.68	0.26-1.80	0.44	0.58	0.17-1.97	0.38	0.30	0.07-1.31	0.11
2. Salivation	7 (8.5)	ne**								
3. Swallowing	6 (7.3)	1.11	0.26-4.70	0.88	1.06	0.16-7.10	0.96	0.85	0.10-7.03	0.85
4. Handwriting	9 (11.0)	1.56	0.60-4.10	0.36	2.07	0.48-8.93	0.33	2.55	0.53-12.30	0.24
5. Cutting food and handling ustensils	15 (18.3)	1.77	0.79-3.96	0.16	2.92	0.64-13.33	0.17	4.88	0.84-28.48	0.08
6. Dressing and hygiene	23 (28.1)	1.47	0.71-3.06	0.30	0.59	0.15-2.28	0.59	0.66	0.13-3.26	0.60
7. Turning in bed and adjusting bed clothes	14 (17.1)	1.29	0.57-2.88	0.53	0.55	0.15-2.02	0.37	0.40	0.10-1.66	0.21
8. Walking	19 (23.2)	2.08	0.99-4.36	0.05	2.78	1.08-7.20	**0.03**	2.84	1.04-7.73	**0.04**
9. Climbing stairs	46 (56.1)	1.13	0.56-2.29	0.74	0.95	0.39-2.28	0.91	1.49	0.57-3.92	0.42
10. Dyspnea	6 (7.3)	1.59	0.55-4.55	0.39	0.97	0.26-3.58	0.96	1.06	0.28-4.00	0.93
11. Orthopnea	0 (0.0)	ne***								
12. Respiratory insufficiency	17 (20.7)	0.69	0.28-1.69	0.42	0.79	0.31-2.06	0.63	0.70	0.22-2.22	0.55
Male sex		1.28	0.62-2.67	0.50				1.47	0.57-3.81	0.43
Bulbar site of onset		1.10	0.52-2.34	0.81				4.06	1.22-13.46	**0.02**
BMI categories				0.23						0.08
Malnutrition		5.07	0.65-39.82					17.97	1.46-221.34	
Normal		1.0						1.0		
Overweight		0.71	0.32-1.57					0.69	0.25-1.96	
Obese		1.71	0.50-5.83					2.61	0.61-11.03	

Age (for 5 years increase)	1.05	0.88-1.24	0.60	0.99	0.79-1.25	0.95
FVC (for 10 units increase)	0.88	0.66-1.16	0.35	0.88	0.59-1.31	0.52

* Abnormal values scored 2 or less for each item, except for item 12 (respiratory insufficiency) for which abnormal values were any score lower than 4; 95% CI : 95% Confidence interval ; ne: not estimated because ** no deaths recorded, *** no patient with abnormal values; BMI: Body mass index, FVC: Forced vital capacity.

Figure 1. Cumulative time-dependent probability of retaining self-sufficiency in the entire sample (n=82)

Figure 2. Cumulative time-dependent survival in non self-sufficient (red) vs. self-sufficient patients (blue) at 4 weeks (p=0.0172)